Attorney Docket No. UAB-15102/22

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jay M. Meythaler et al.

Serial No.: 10/049,327 Group Art Unit: 1617

Filing Date: May 15, 2002 Examiner: Kathrien Ann Cruz

For: METHOD OF TREATING TRAUMATIC BRAIN AND SPINAL CORD INJURIES AND OTHER NEUROGENIC CONDITIONS USING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND NATURALLY OCCURRING CONOTOXINS

PRE-APPEAL BRIEF REQUEST FOR REVIEW
STATEMENT OF ARGUMENTS

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants request review of the above-referenced application on the basis of the following remarks.

Claims 1, 29, and 36 remain rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the enablement requirement on the basis that "[i]n order to make all forms of prodrugs would require an extensive amount of experimentation to determine that the active sites of such prodrugs are effective in the treatment of inflammation." (Paper No. 20091109, page 3.) Underlying this assertion is Examiner's finding that there are no working examples of "solvates or hydrates;" the unpredictable nature of pharmacokinetics in humans, and a single reference that asserts difficulties in extrapolating between species and a lack of a standard pharmacokinetic protocol. *Id.*, paragraph bridging pages 5-6.

Claims 1, 7, 29, 34-36, and 40 remain rejected under 35 U.S.C. §103(a) over Breitner (US 5,643,960) in view of Bustamante (JPET, 1997; 281:1381-1391) and Grilli (WO 98/20864) on the

basis that choline magnesium trisalicylate (CMT) is an art recognized equivalent of other NSAIDs including ASA and the prior art teaches CMT for the prevention of Alzeheimer's disease or related neurodegenerative disorders. (See *Id.* at pages 8-9.)

Remarks directed to the rejection of claims 1, 29, and 36 under 35 U.S.C. §112, first paragraph, enablement.

Examiner considers page 21 of the specification as the only teaching applicable to prodrugs. (See Paper No. 20091109, page 5.) To the contrary, the art recognizes more than just solvates or hydrates of a parent compound as prodrugs. A prodrug is defined as one that is converted into a different form in an organism. This is exemplified by the definition of prodrug in the subject specification at page 19, lines 16-18. For example, esters of a particular compound are also prodrugs. The subject specification provides several examples of esters of CMT on page 19, lines 3-8 and indicates that typical methods of preparation are known in the art and applicable to CMT. These esters represent numerous examples of prodrugs. Typically solvates and hydrates, as exemplified by Examiner, are forms of either a parent compound or a prodrug and do not create a prodrug from a parent compound. No specific example of a solvate or hydrate is required for enablement given the numerous examples of prodrugs taught in the specification.

In addition, the specification provides ample guidance on pages 19-20 through two detailed publications illustrating how to make and use prodrugs are incorporated by reference for this purpose. The subject specification cites T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and "Bioreversible Carriers in Drug Design," ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987 for the considerations required to synthesize a prodrug of CMT. As such, a person of ordinary skill in the art has ample guidance as to how to make and use prodrugs of CMT.

Further, even if this guidance were not presented, the mere fact that making a compound requires experimentation does not render it non-enabled as long as the experimentation is not undue. The rejection asserts that predicting metabolism from a prodrug to an active species is "filled with experimental uncertainty," and that predicting drug metabolism "is still an experimental science." (Paper No. 20091109, page 5.) The question under 35 U.S.C. §112 is not whether experimental certainty exists, but instead whether any experimentation is undue. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such

experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In *In re Certain*, the court found that determining the cell culture conditions and cell types suitable for use with culturing surface beads with a charge capacity of less than 0.9 meq/g was not undue experimentation. In that case a practitioner needed to analyze various buffer conditions, nutrient supplements, atmospheric conditions, culture temperature, and even determine whether the invention would work with any desired cell type. Even with this large array of experimental variables, the experimentation was not held undue because the art typically engages in cell culturing. *Id.*

The experimentation required for the inventions of claims 1, 29, and 36 require fewer experimental variables and are also customarily practiced. At the time of filing, those of skill in the art routinely and regularly designed modifications to drugs for metabolization by the body. Studies in pharmacokinetics are daily if not hourly events in any pharmaceutical laboratory. These studies require only three steps: 1) make the compound; 2) administer the compound; and 3) determine parent and metabolite concentration as a function of time. A person of ordinary skill in the art recognizes how to dose an organism with a compound, how and when to take biological samples, and how to determine bioavailability from drug concentration typically determined by mass spectrometry. Any required experimentation is not undue, it is routine.

In view of the foregoing remarks, Applicants submit that a person of ordinary skill in the art has ample guidance concerning how to make and use a prodrug of CMT. Reconsideration and withdrawal of the rejections of claims 1, 29, and 36 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Remarks directed to rejection of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) over Breitner in veiw of Bustamante and Grilli.

The cited prior art combination of Breitner in view of Bustamante and Grilli fails to provide any reasonable expectation of success for the treatment of neurotrauma or inflammation associated with neuronal injury with choline magnesium trisalicylate (CMT).

The basis of the outstanding rejection is that Breitner teaches "a method of delaying the onset of Alzheimer's disease or related neurodegenerative disorders" with NSAIDs such as choline

magnesium trisalicylate. (Paper No. 20091109, page 8.) (emphasis added, and omitted) Grilli is cited as teaching treatment of Alzheimer's disease or neuronal damage related to Alzheimer's disease with NSAIDs. (Paper No. 20091109, page 3-4 and 9 (citing Abstract).) All NSAIDs are cited as equivalents in Grilli at page 9 of Paper No. 20091109 ("[T]he NSAIDs show a protective activity against glutamate-induced neurotoxicity.")

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). A person of ordinary skill in the art has no reasonable expectation of success from the teaching of Breitner alone or in combination with Bustamante and Grilli.

Breitner does not teach treatment of neurotrauma or neuronal injury. The entire underlying purpose of Breitner is to analyze past use of an NSAID and its correlation with subsequent onset of Alzheimer's disease.

Grilli similarly teaches prevention. Only ASA or NaSal are stated for treatment in Grilli at cited paragraph page 3, lines 11-14. The present claims are not directed to ASA or NaSal. They are directed to CMT and prodrugs thereof. Grilli teaches that all NSAIDs are not equivalent with respect to treatment even assuming they are equivalent with respect to prevention. Grilli teaches that indomethacin (another NSAID) was "unable to prevent glutamate-evoked cell death." (page 9, lines 10-13.) Thus, Grilli making the unsupported statement that ASA of NaSal are effective treatments of Alzheimer's disease does not lead one of ordinary skill in the art to other NSAIDs or specifically to CMT for treatment of neurotrauma or neuronal injury.

A person of ordinary skill in the art has no reasonable expectation of success in modifying Breitner to administer CMT or any other NSAID for use as a therapeutic for the treatment of neurotrauma. The mechanisms of treatment and prevention are entirely unique. Breitner associates delayed disease onset with past use. No data, chart, statement, or suggestion in Breitner indicates that the unique properties of CMT such as Ca^{2+} effects and amelioration of remote secondary damage resulting from neurotrauma are necessary or have any role in prevention. Further, one of ordinary skill in the art recognized at the time of filing from animal experiments that treatment of neurotrauma with an NSAID was ineffective. The subject specification teaches: "Up to now, drugs have been used that are only marginally effective in preventing this cascade of events and non-steroidal

inflammatory drugs (NSAIDS) have not been useful in animal models for neurotrauma." (page 8, lines 11-14.) The specification teaches that this may be due to inhibition of platelet function, a process which is not differentiated by or a problem in Breitner, Bustamante, or Grilli. Indeed, Breitner states that COX-2 selective compounds such as naproxen are equally preferred to non-selective compounds such as sulindac. (col. 3, lines 52-61.) Thus, Breitner teaches that selectivity is not necessary. Further, Breitner teaches that aspirin "alone appeared to produce weak but similar effect to NSAIDs" also suggesting that selectivity is not required. (col. 8, lines 54-55.) Aspirin is not useful for the treatment of neurotrauma at least because it will increase bleeding – a wholly undesirable side effect following trauma. Overall, a person of ordinary skill in the art concludes that the mechanisms of prevention are entirely different form the mechanisms of treatment such that success in prevention does not equate to success in treatment.

The lack of any reasonable expectation of success flows directly from the data of Breitner itself. In each case, those treated with NSAIDs who had Alzheimer's disease were diagnosed with the same disease state as those who received no treatment. As such, a person of ordinary skill in the art reads Breitner as suggesting that there is no therapeutic benefit to administration of any NSAID, if one had actually been administered after disease onset.

In view of the above remarks, reconsideration and the withdrawal of the rejections of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) over Breitner in view of Bustamante and Grilli is solicited.

Dated: February 24, 2010

Respectfully submitted,

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